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### REMARKS

Claims 11-30 are currently pending in the present application.

At the outset, Applicant would like to draw the Examiner's attention to the Burdick reference. The Examiner has relied upon European Patent Publication No. EP1004594A1 of Burdick, *et al* (hereinafter referred to as "Burdick"), in making the obviousness rejection set forth in Paper No. 9, at ¶2, page 5, and in Paper No. 7, at ¶2, page 4. However, the Burdick reference has not been made of record in the instant application. Applicant has not cited Burdick, nor has the Examiner listed Burdick on a Form PTO-892. Moreover, Burdick has a publication date of May 31, 2000, and thus, does not even qualify as prior art against the instant application which was filed as an International Application on November 5, 1998. Applicant attempted to bring this fact to the attention of the Examiner in Applicant's Response filed on March 19, 2001. (See, Applicant's Request for Reconsideration submitted via facsimile on March 19, 2001, 2<sup>nd</sup> full paragraph of page 7). However, since the Examiner insists upon relying on the teachings of Burdick in formulating the rejection mentioned above, as set forth in Papers No. 7 & 9, the reference should have been listed on a Form PTO-892. In an effort to ensure that this reference appears on the face of any patent which issues based upon the instant application, Applicant has enclosed a copy of a Form PTO-1449 listing Burdick for the Examiner's convenience. Applicant respectfully requests that the Examiner enclose an initialed copy of the enclosed Form PTO-1449 along with her next communication to Applicant's undersigned representative, clearly indicating consideration of the listed reference. Also listed on the enclosed Form PTO-1449 are Attachments A & B, referenced below and attached hereto. Applicant respectfully requests that the Examiner acknowledge receipt and consideration of said Attachments.

Also, Applicant would again like to draw the Examiner's attention to, and specifically point out an error concerning an alleged election of species. In Paper No. 7, at page 3, line 9, and in Paper No. 9, at page 4, line 2, the Examiner states, "[s]ee Fig. 2 for the elected species eicosapentaenoic acid." Applicant respectfully notes that no Species

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Election Requirement has been issued in the instant case. Accordingly, no election of any particular species has been made. Moreover, eicosapentaenoic acid is not conjugated, and thus, is not a species within the genus "conjugated fatty acids". Any limitation of search, scope or meaning which may be attributable to an election of species is improper in the instant application. Applicant respectfully requests acknowledgement of this error by the Examiner.

#### Overview

Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness with respect to any of the pending claims, based upon any of the cited references. Applicant respectfully submits that the Examiner's argument necessarily likening "monoenes and polyenes" and "n-3/n-6 omega fatty acids" to *conjugated* fatty acids is incorrect. Furthermore, Applicant again notes that Burdick does not qualify as prior art under 35 U.S.C. §102. Moreover, Applicant respectfully submits that even if the Examiner had established a *prima facie* case of obviousness, which she has not, any such *prima facie* case of obviousness would be overcome by Applicant's showing of unexpected and significantly improved results, as evidenced in Applicant's Specification.

Applicant respectfully reiterates his previous assertion that the Examiner has failed to satisfy all of the well-settled criteria required to establish a *prima facie* case of obviousness. Furthermore, Applicant respectfully submits that the Examiner has entirely ignored the indicia of non-obviousness set forth in Applicant's Specification, as referenced in Applicant's Response filed on March 19, 2001. It is submitted that the Specification sufficiently evidences the unexpected and significantly improved results obtained in conjunction with Applicant's invention, and thus overcomes any alleged *prima facie* case of obviousness.

Each of the two outstanding rejections, as set forth in Paper No. 7 and maintained in Paper No. 9, will be addressed initially and separately, addressing the Examiner's failure to establish a *prima facie* case of obviousness in each instance. Subsequently, this response addresses the indicia of non-obviousness set forth in the Applicant's Specification.

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**Rejection Under 35 U.S.C. §103(a) Over Miettinen, In View of Alexander**

In Paper No. 9, the Examiner reiterates her rejection of claims 11-30 under 35 U.S.C. §103(a), as being unpatentable over European Patent Application No. EP0594612 of Miettinen, *et al.* ("Miettinen"), in view of Alexander Leaf, *et al.*, "Medical Progress: Cardiovascular Effects on n-3 Fatty Acids", THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 318, No. 9, pages 549-557 (March 3, 1988), (referred to as "Alexander, *et al.*" by the Examiner, and hereinafter referred to synonymously as "Leaf" and "the Leaf Article"), and makes the rejection final.

In Paper No. 9, the Examiner reiterates her contention that Miettinen teaches a "fatty acid composition of  $\beta$ -sitostanol ester mixtures containing large amount [sic] of monoenes and polyenes", and that Miettinen teaches an enhanced efficacy of such compositions in lowering serum cholesterol levels, citing lines 40-45 and 56-68 of page 4, and Examples 1-3. (See, Paper No. 9, p. 3 (*emphasis added by Examiner*)). The Examiner again acknowledges that Miettinen fails to teach phytostenol esters of conjugated acids, or the use thereof in reducing serum cholesterol levels. (See, Paper No. 9, p. 3). However, the Examiner again contends that the Leaf Article teaches "n-3 fatty acids for lowering the low-density lipoprotein (LDL) cholesterol", citing the last paragraph of column 2, at page 549. (*Id.*). The Examiner argues that this disclosure somehow alleviates the deficiencies of Miettinen. The Examiner also reiterates all of her previous assertions and contentions concerning the references and their teachings, as set forth in Paper No. 7.

In Paper No. 9, the Examiner responds to Applicant's arguments set forth in the Response filed on March 19, 2001, by acknowledging Applicant's argument that Miettinen does not teach conjugation. The Examiner then notes her disagreement with Applicant's argument "because polyenes and monoenes are conjugated." (Paper No. 9, page 2).

Applicant strenuously, but respectfully, traverses the Examiner's rejection and the arguments and contentions in support thereof, as explained in more detail below.

First, there is no teaching or suggestion in either of the references of phytostenol esters of conjugated fatty acids. Contrary to the Examiner's assertion, polyunsaturation does not

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necessarily require conjugation. Second there is no teaching or suggestion in either of the references which would motivate one of ordinary skill in the art to combine and modify the teachings of the cited references to arrive at Applicant's invention. Third, one of ordinary skill in the art would have no reasonable expectation of success when neither reference teaches or suggests esters of conjugated fatty acids.

It is well-settled that in order to establish a *prima facie* case of obviousness, and thus shift the burden of proving non-obviousness onto Applicant, the Examiner must show all of the following three criteria: (1) there must be some suggestion or motivation to modify or combine the references as suggested by the Examiner (it is not sufficient to say that the cited references can be combined or modified without a teaching in the prior art to suggest the desirability of the modification); (2) there must also be a reasonable expectation of success; and (3) the references as combined must collectively teach or suggest all limitations of the claims. The teaching or suggestion to combine and modify the cited art and the reasonable expectation of success: must both be found in the prior art and not in the Applicant's Specification. (M.P.E.P. §2143).

None of the three criteria necessary to establish such a *prima facie* case of obviousness has been satisfied.

Prior to addressing each of the required criterion, Applicant would like to take this opportunity to restate certain broad aspects of his invention, and reiterate the surprising and significantly improved results thereof. One aspect of Applicant's claimed invention is directed to methods of reducing serum cholesterol content in a mammal, comprising: (i) providing a hypocholesteremic preparation comprising at least one phytosterol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms; and (ii) administering the hypocholesteremic preparation to a mammal in an amount effective to reduce serum cholesterol content in the mammal. Another aspect of Applicant's claimed invention is directed to hypocholesteremic preparations comprising at least one phytosterol ester of a conjugated fatty acid having from about 6 to about 24 carbon atoms. Hypocholesteremic preparations, and methods for their use, in accordance with Applicant's claimed invention surprisingly exhibit significantly improved

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cholesterol reducing activity over phytosterol derivatives derived from non-conjugated fatty acids. (See, e.g., Applicant's Specification, page 2, lines 22-29). It is a significant advantage to use a phytosterol ester having such increased activities when preparing foodstuffs, where increased concentration of additives, such as phytosterol esters, can negatively affect the taste and/or other aesthetic properties of the foodstuff. (See, e.g., Applicant's Specification, page 2, lines 1-5).

With respect to the alleged *prima facie* case of obviousness, Applicant would first like to point out that neither reference teaches or suggests phytosterol esters of conjugated fatty acids. The Examiner has argued that "polyenes and monoenes are conjugated." (Paper No. 9, page 2). On this basis, the Examiner has argued that the reference to "polyenes and monoenes" in Miettinen provides a suggestion of the claimed esters of conjugated fatty acids. Applicant respectfully disagrees. For the Examiner's convenience, Applicant has attached (as Attachment A) the definitions of (i) "conjugated fatty acid" and (ii) "conjugated double bonds". As indicated on page 306 of Attachment A, a conjugated fatty acid is simply a fatty acid containing conjugated double bonds. Additionally, as indicated on the same page of Attachment A, conjugated double bonds are "two or more double bonds which alternate with single bonds in an unsaturated compound, ...". (See, Attachment A: Richard J. Lewis, Sr. (Rev'd By), Hawley's Condensed Chemical Dictionary, Twelfth Edition, pages 306 & 932 (1993). (4 pages), (*emphasis added*)). Thus, by definition, a monoene cannot be conjugated. There is only one double bond in a *monoene*. Applicant has also attached, on page 932 of Attachment A, the definition of (iii) a "polyene". As indicated on page 932 of Attachment A, a polyene is "any unsaturated aliphatic or alicyclic compound containing more than four carbon atoms in the chain and having at least two double bonds." (See, *id.*, at page 932). There is no mention of conjugation. There is no suggestion that the term polyene, by definition, includes compounds having at least two double bonds which alternate with single bonds. In fact, when referring to conjugated compounds, the term "conjugated" is expressly used. As used in Miettinen, the phrase "large amounts of monoenes and polyenes" refers to the total content of unsaturated components in a vegetable oil, and includes monounsaturated fatty acids and polyunsaturated fatty acids. (See, Miettinen, page

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4, line 41). The phrase has no relation to *conjugated* fatty acid species, which are not simply polyenes, but compounds that contain at least two double bonds which alternate with single bonds.

Thus, regardless of the Examiner's broad assertion that Miettinen teaches  $\beta$ -sitostanol fatty acid ester mixtures containing large amounts of monoenes and polyenes, Applicant maintains that Miettinen does not teach or suggest phytosterol esters of a conjugated fatty acids having from about 6 to about 24 carbon atoms.

In fact, Miettinen only notes that "the  $\beta$ -sitostanol fatty acid ester mixture *can be selected* so as to contain large amounts of monoenes and polyenes, . . ." (Page 4, lines 40-41, (*emphasis added*)). Miettinen makes no mention of conjugation. Moreover, Miettinen provides no further guidance as to how the mixture "can be selected" so as to contain monoenes and polyenes. Miettinen discloses the use of vegetable oils in general, and specifically mentions rapeseed oil, coconut oil, sunflower oil, soybean oil, olive oil and corn oil. It is respectfully submitted that most common vegetable oils, in general, do not contain any significant amounts of conjugated fatty acids. For the Examiner's convenience, Applicant has submitted herewith Attachment B: Daniel Swern, (*Ed.*), Bailey's Industrial Oil and Fat Products, Vol. 1, Fourth Edition, pages 31, 34-36 (1979) (6 pages). As indicated in Table 1.7 on page 31 of Attachment B, the majority of polyunsaturated fatty acids found in vegetable oils (*e.g.*, safflower, sunflower, cottonseed, linseed, perilla, and other drying oils and seed fats) are linoleic and linolenic oils, which are not conjugated. A common conjugated fatty acid, *i.e.*, eleostearic acid, is prevalent in tung oil. Miettinen simply does not teach esters of phytosterols and conjugated fatty acids, nor does the reference suggest such esters. Reference to unsaturation does not, by itself, require any conjugation. Moreover, reference to polyunsaturation does not necessarily mean that any conjugation exists.

Secondly, Applicant respectfully submits that the Examiner's arguments pertaining to the Leaf Article are also incorrect, and inaccurate. The Examiner argues that the Leaf Article "alleviates the deficiency of Miettinen *et al.* because it teaches the n-3 fatty acids for lowering the low-density lipoprotein (LDL) cholesterol." (See, Paper No. 9, p. 3). While the

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Examiner is correct that the Leaf Article teaches lowered levels of LDL cholesterol in the blood of Eskimos whose diets included large amounts of long chain n-3 polyunsaturated fatty acids, which are commonly found in the fish which make up a large portion of the Eskimos' diet, this teaching is not adequate to alleviate any of the deficiencies of the Miettinen reference. The polyunsaturated n-3 and n-6 fatty acids disclosed in the Leaf Article are not conjugated. The beneficial n-3 fatty acids disclosed in the Leaf Article are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). (See, Leaf, page 549, col. 1, lines 17-20). The structural formulas for both EPA and DHA are set forth in Figure 1, on page 550 of the Leaf Article. The existence of two single carbon-carbon bonds between each unsaturation in the formulas presented in Figure 1 specifically indicates that there is no conjugation in either EPA or DHA. Furthermore, as specified at page 36 of Attachment B, the structures of EPA and DHA found in marine oils have been confirmed as 5,8,11,14,17-eicosapentaenoic acid and 4,7,10,13,16,19-docosahexaenoic acid. (See, Daniel Swern, (Ed.), Bailey's Industrial Oil and Fat Products, Vol. 1, Fourth Edition, pages 31, 34-36 (1979)). As clearly indicated by the structural nomenclature, none of the double bonds are conjugated.

The Leaf Article is directed to the effects of n-3 and n-6 polyunsaturated fatty acids. The designations, "n-3" and "n-6", simply refer to the number of carbon atoms from the methyl-terminus of the fatty acid at which the first unsaturation is located. Again, none of the fatty acids identified in the Leaf Article is conjugated. As previously pointed out in Applicant's response filed on March 19, 2001, the linoleic acid shown in Figure 1 of the Leaf Article is 9,12 linoleic acid. The  $\alpha$ -linolenic acid is 9,12,15-linolenic acid. Conjugation of said acids would require double bond locations at 9,11 and 9,11,13 respectively. The Leaf Article focuses on the differentiation in the body between n-3 and n-6 polyunsaturated fatty acids. There is no teaching or suggestion in the Leaf Article to ingest conjugated fatty acids, nor any teaching or suggestion that such ingestion could be undertaken to reduce serum cholesterol levels.

The Examiner appears to address the lack of any express teaching with respect to conjugated fatty acids by noting that the Leaf Article also mentions "dietary fish and fish oil supplements". (*Id.*). Again, while the Leaf Article clearly references fish which contain the

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taught n-3 fatty acids, the reference makes no mention of any conjugation, and as indicated above, Attachment B notes the structure of such acids derived from marine oils as being non-conjugated.

Moreover, as the Leaf Article specifically teaches the benefit of n-3 polyunsaturated fatty acids, all of which are not conjugated, it would appear that Leaf actually teaches away from hypocholesteremic preparations containing conjugated fatty acids, and instead focuses on the value of the more common, or more regular, "9,12" and "9,12,15" polyunsaturated fatty acids.

Thus, Applicant again submits that neither reference, nor a combination thereof, teaches or suggests each and every element of the claimed invention. Specifically, neither reference teaches the use of conjugated fatty acids in lowering serum cholesterol levels. Moreover, neither reference teaches the use of an ester of a phytosterol compound with a conjugated fatty acid for such a purpose.

Next, Applicant submits that neither Miettinen, nor the Leaf Article, either alone or in combination, contains any teaching or suggestion which would motivate one of ordinary skill in the art to combine and modify their teachings, as suggested by the Examiner, in order to arrive at the claimed invention. As discussed above, neither reference teaches the use of conjugated fatty acids. Absent any specific teaching to use esters of conjugated fatty acids, it cannot reasonably be said that one of ordinary skill in the art would be motivated to modify the references to include the use of such esters. Moreover, based upon Leaf's apparent emphasis on non-conjugated acids, it could be said that the reference teaches away from the suggested modification.

Finally, given the lack of any teaching or suggestion of conjugated fatty acid esters of phytosterol compounds, and given the lack of any teaching or suggestion motivating such a modification of the prior art, one of ordinary skill in the art would not have a reasonable expectation of success, based upon the cited art.

Accordingly, Applicant submits that the Examiner has failed to establish a *prima facie* case of obviousness, as none of the three criteria necessary to establish a *prima facie* case



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of obviousness has been satisfied. Thus, Applicant respectfully requests withdrawal of the rejection based upon Miettinen and the Leaf Article.

**Rejection Under 35 U.S.C. §103(a) Over Burdick**

In Paper No. 9, the Examiner reiterates her rejection of claims 11-30 under 35 U.S.C. §103(a), as being unpatentable over European Patent Application No. EP1004594 of Burdick, *et al.* ("Burdick"), and makes the rejection final. As mentioned at the outset, Applicant again notes that the Examiner has failed to list Burdick on a Form PTO-982. The Examiner has made several contentions and arguments with respect to the teachings of Burdick, specifically with respect to how such contended teachings somehow suggest Applicant's claimed invention.

While not agreeing with any of the Examiner's contentions or arguments in this regard, Applicant respectfully traverses this rejection on the basis that Burdick is not prior art. Burdick, European Patent Publication No. EP1004594A, published on May 31, 2000. The instant application has an International Filing Date of November 5, 1998. Burdick does not qualify as prior art under 35 U.S.C. §102, and thus, cannot form a proper basis for a rejection under 35 U.S.C. §103(a). Applicant respectfully requests withdrawal of the rejection based upon Burdick.

Even if Burdick qualified as prior art under 35 U.S.C. §102, which it does not, it still fails to teach or suggest each and every element of Applicant's claimed invention. Burdick references omega-3 polyunsaturated fatty acids (*i.e.*, n-3 fatty acids), and specifically mentions EPA and DHA. (See, Burdick, ¶ 0013). However, as discussed above in relation to the Leaf Article, neither EPA nor DHA is conjugated. Moreover, Burdick makes no mention of conjugation, nor does Burdick contain any teaching which would suggest the desirability of using a conjugated fatty acid.

Thus, Burdick fails to satisfy any of the three criteria necessary to establish a *prima facie* case of obviousness.

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Indicia of Non-Obviousness

Even if it were assumed, for argument's sake, that a *prima facie* case of obviousness could be established based upon any of the cited references, or a combination thereof, and that such a *prima facie* case of obviousness had been established, which it cannot and has not, any such alleged *prima facie* case of obviousness would be overcome by Applicant's showing of unexpected, significant improvements.

As evidenced by the Examples set forth in Applicant's Specification, beginning at page 8, line 31, the phytosterol esters of conjugated fatty acids in accordance with certain preferred embodiments of Applicant's invention exhibit significant cholesterol reducing properties. The amount of cholesterol level reduction is significantly greater than phytosterol esters of non-conjugated fatty acids. As can be seen from Table 1, esters of conjugated fatty acids performed significantly better than polyunsaturated acid esters with no conjugation (such as those of linoleic acid). These significant improvements are surprising as noted in the Specification. Applicant's Specification specifically states:

Surprisingly, it has been found that phytosterol esters based on conjugated fatty acids exhibit, with respect to reducing the cholesterol content in the blood, considerably higher activity than comparable phytosterol esters derived from saturated fatty acids, monounsaturated fatty acids or polyunsaturated fatty acids having two or more unconjugated double bonds.

(See, Applicant's Specification, page 2, lines 22-29).

Additionally, as the Examiner is aware, the Federal Circuit has held that "the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results." (*In re Soni*, 34 USPQ 2d 1684, 1687 (Fed. Cir. 1995) (*emphasis added*), citing *in re Margolis*, 228 USPQ 940 (Fed. Cir. 1986)). The Federal Circuit also held that, "when an applicant demonstrates *substantially* improved results, . . ., and states that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." (*Soni*, at 1688 (*emphasis in original*)).

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It is submitted that Applicant's showing of unexpected and improved results sufficiently rebuts any alleged *prima facie* case of obviousness. Therefore, withdrawal of all rejections under 35 U.S.C. §103(a) is respectfully requested.

**Conclusion**

In view of the remarks set forth above, Applicant submit that all pending claims parentably distinguish over the prior art of record and known to Applicant, either alone or in combination. Accordingly, reconsideration, withdrawal of the rejection and a Notice of Allowance are respectfully requested.

Respectfully submitted,

**BERND FABRY**

November 5, 2001  
(Date)

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Enclosures:

- (1) Form PTO-1449 (1 page)
- (2) Attachment A: Richard J. Lewis, Sr. (*Revsd By*), Hawley's Condensed Chemical Dictionary, Twelfth Edition, pages 306 & 932 (1993). (4 pages)
- (3) Attachment B: Daniel Swern, (*Ed*), Bailey's Industrial Oil and Fat Products, Vol. 1, Fourth Edition, pages 31, 34-36 (1979). (6 pages)

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